REMARKS

Claims 1, 2, and 6 – 19 are under examination.

Rejection Based on Obviousness-type Double Patenting

Claims 1, 2 and 6-10 were rejected on grounds of obviousness-type double patenting over claims of a number of U.S. patents and an allowed U.S. application.

In particular, claims 1, 2 and 6-10 were rejected on grounds of obviousness-type double patenting over claims 22-25 of U.S. 6,368,636.

In response, Applicants note that claim 1 of the application is drawn to administration of MSCs, without prior MHC matching, to promote hematopoietic cell engraftment whereas claims 22-25 of the '636 patent are drawn to "transplanting to a transplant recipient a transplant treated with a supernatant of mesenchymal stem cells" [emphasis added] wherein prior MHC matching may not be a routine part of the procedure. Thus, regardless of whether the supernatant can stand in for the cells is irrelevant. These are different procedures (administration to a graft recipient versus treating the transplanted tissue *ex vivo* prior to engraftment) and Applicants do not believe they are obvious variations of each other.

Also in particular, claims 1, 2 and 6-10 were rejected on grounds of obviousness-type double patenting over claims 1-22 of U.S. 6,328,960.

In response, Applicants note that claim 1 of the application is drawn to administration of MSCs, without prior MHC matching, to promote hematopoietic cell engraftment, such as by forming new marrow stroma, whereas claims 21 of the '960 patent are drawn to "transplanting to a transplant recipient a transplant treated with

mesenchymal stem cells" [emphasis added]. These are different procedures (administration to a graft recipient versus treating the transplanted tissue *ex vivo* prior to engraftment) and Applicants do not believe they are obvious variations of each other.

As to claim 1 of the '960, Applicants' claim 1 is directed to promoting engraftment of hematopoietic cells and progenitor cells and not to reducing response of an effector cell against an alloantigen and where the MSCs may be administered absent any prior MHC matching step. This is amply described in the application at page 10, lines 3-15, such as where the MSCs are administered intravenously and find their way to the marrow to produce progenitor cells and regenerate stroma. Conversely, the claims of the '960 patent, which do not recite absence of any matching step, are directed to reducing activity of effector cells against an alloantigen and thereby preserving the integrity of a graft, such as an allograft, but such claimed methods do not rely on the MSCs promoting engraftment or forming new marrow stroma without pre-matching.

Also in particular, claims 1, 2 and 6-10 were rejected on grounds of obviousness-type double patenting over claims 1-3 and 8-10 of U.S. 6,797,269.

In response, Applicants note that claim 1 of the application is drawn to administration of MSCs, without prior MHC matching, to promote hematopoietic cell engraftment, such as by forming new marrow stroma, whereas claims 13 and 8-10 of the '269 are directed to inhibiting a T-cell response to an antigen. Applicants respectfully contend that these inventions are not obvious variations of each other for the reasons already cited.

Also in particular, claims 1, 2 and 6-10 were rejected on grounds of obviousness-type double patenting over claims 1-20 of U.S. 2002/0085996, now allowed.

In response, Applicants note that U.S. Serial No. 10/067,121 has now issued as U.S. 6,875,430 with claims 1-20 all drawn to methods of reducing response of effector cells against xenoantigens.

The below-named agent is also the agent for this newly issued '430 patent. This '121 application was last in a chain that included the applications that issued as the aforementioned '636 and '960 patents already discussed above. Claims 1-20 of the '121 application on which the '430 patent is based (relied on by the Examiner herein) cannot now issue because they were canceled from the '121 application (said claims having issued in the '636 and '960 patents) and no continuing application based on the '121 application has been filed.

Rejection Under 35 U.S.C. 102

Claims 11 to 13 were rejected as anticipated by Abatangelo et al (US 6,482,231), which is said to teach introducing into a patient a preparation of mesenchymal stem cells and a three dimensional matrix carrier.

In response, Applicants first note that Abatangelo et al teaches only transplanting MSCs with a 3 dimensional matrix. Applicants' claim 11 is directed to a method of promoting muscle growth and, for this purpose, the application teaches use of methods other than with a 3 dimensional matrix. Thus, Applicants have amended claim 11 to recite these alternative methods of administration (i.e., infusion or direct injection), neither of which involves use of a preformed 3 dimensional matrix containing said MSCs (which is all that Abatangelo et al teach. In addition, Applicants also note that claim 11 is directed to human treatment and, in such cases, a step of prior matching of transplant cells to the recipient is commonly used whereas in Applicants' claim 11 no such stem is employed.

Applicants also note that claims 14 (systemic administration) and 15 (intravenous) are forms of infusion or direct injection and thus still properly depend from claim 13. Applicants have also added new claim 20 drawn to direct injection into muscle tissue.

Support for these amendments and new claim 20 is found throughout the application, especially at page 7, lines 17-19, and at page 13, line 31, to page 14, line 2.

Claims 1, 2, and 6-10 were rejected under 35 U.S.C. 102(f) on grounds that Applicants did not invent the claimed subject matter. The Examiner cites US 6,368,636, US 6,328,960, US 6,797,269 and allowed US application 10/067,121.

In response, Applicants note that the cited patents do not disclose the essential feature recited in Applicants' claim 1 that the human MSCs can be administered without a step of MHC matching prior to said transplant, a step which is always utilized for human tissue and organ transplants. None of the cited patents teaches that this step can be discarded. In addition, Applicants believe that the cited patents and application recite inventions patentably different from those of claim 1 herein for the reasons cited above with respect to obviousness-type double patenting, which arguments Applicants reiterate here.

Rejection Under 35 U.S.C. 103

Claims 16 were rejected under 35 U.S.C. 103(a) as being unpatentable over Abatangelo et al (U.S. 6,482,231) as applied to claims 11-13 and further in view of Gerson et al (U.S. 5,591,625).

A finding of obviousness requires three conditions:

1. The cited references, in light of the then available general knowledge, must suggest the combination of the references to produce the claimed invention [see: *In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988)].

2. Combination or modification of the references must have a reasonable expectation of success. [See: *Amgen v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209 (Fed. Cir. 1991)]

3. Combination of the cited references must teach or suggest all of the limitations of the claim(s) [See: *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970)]

Applicants respectfully urge that, at the least, points 1 and 3 are not satisfied. Point 3 is not satisfied because the application at page 1, last paragraph, teaches that "the mesenchymal stem cells are immunologically neutral and therefore can be used as described herein without inducing an adverse immune response in the recipient of the cells." Since this was not previously known, there was no reasonable expectation that allogeneic mesenchymal stem cells could be used without provoking an adverse immune response associated with the use of such material so that an essential limitation (no prior MHC matching) recited in the method of claim 11 (from which claim 16 depends) is not satisfied.

Combination of Abatangelo et al with Gerson does not achieve Applicants' invention since, like Abatangelo, Gerson does not disclose or suggest that mesenchymal stem cells do not produce an adverse immune response. In fact, Gerson states "Patient preparation for introduction of mesenchymal stem cells includes, but is not limited to...(c) immunosuppression in the setting of allogeneic cell therapy." [See column 2, lines 62-67]. No one but the inventors of the present invention have discovered the ability to use allogeneic cells without prior matching or immunosuppression. In sum, since it would not have been obvious to transplant

allogeneic mesenchymal stem cells not having genetic modification and not using the artificial 3 dimensional support, it would be equally unobvious to transplant such cells following genetic modification.

In addition, point 1 is not met because the references cannot be combined to achieve the invention of claim 16 (which must include all limitations of claim 11) because Abatangelo et al teach only use of an artificial 3 dimensional support, which is not encompassed by amended claim 11 (from which claim 16 depends), and any combination of Gerson's recombinant cells (i.e., cells expressing a therapeutic gene) with the teaching of Abatangelo et al must also result in reliance on such a support. Therefore, combination of these references cannot achieve the invention of amended claim 11 regardless of whether wild type or recombinant MSCs are employed because claim 11 does not encompass use of an artificial 3 dimensional support.

Rejection Under 35 U.S.C. 112

Claim 13 was rejected under 35 U.S.C. 112, paragraph 2, as being indefinite for lack of antecedent basis.

In response, Applicants have amended claim 13 to depend from claim 12 instead of claim 11, wherein claim 12 does recite use of a cell preparation. Applicants believe such amendment avoids this ground of rejection.

Claim Objections

Claim 1 has been amended to insert "the" before "recipient" in place of "a" so as to overcome the objection.

Claims 2, 6-10, 12-16, 18 and 19 have all been amended to insert a comma before the word "wherein" so as to avoid the objection.

Claim 6 was amended to insert the word "recipient" before "mammal" and thus overcome the objection.

Claim 11 was amended to insert "the" before "recipient" in place of "a" so as to overcome the objection.

Claim 17 was amended to insert the word "tissue" before the word "surface" and insert "the" before "recipient" in place of "a" and insert the word "stem" before the word "cells" so as to overcome the objection.

In view of the foregoing response and amendments, Applicants believe that the grounds of rejection have been overcome and respectfully request that the Examiner reconsider the rejection.

Applicants have included herewith a request for a 1 month extension of time to respond and a check covering all fees for a small entity. No additional fee is believed due in filing the above amendment. The Commissioner is requested to charge any additional fees, or credit any refunds, to Deposit Acc't No. 03-0678.

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